

Supplementary Table S1¹

PICO 1. In patients with MDR/RR-TB, which individual drugs in the regimens are more or less likely to lead to treatment success (and other relevant outcomes)?

PICO 2. In TB patients with isoniazid-resistant TB or *M.bovis* disease, which drug regimen composition and duration is more or less likely to lead to treatment success (and other relevant outcomes)?

PICO 3. In MDR-TB patients, are treatment regimens lasting up to 12 months more or less likely to lead to treatment success (and other relevant outcomes), when compared with those recommended in the WHO guidelines of 2011?

PICO 4. Among patients on MDR-TB treatment, is the (i) timing to start of treatment and (ii) elective surgery more or less likely to lead to treatment success (and other relevant outcomes)?

PICO=Population, Intervention, Comparator to the intervention, Outcomes

¹ see Annex 3 of (25) for the full versions of the PICO questions

Supplementary Table S2. Summary of the evidence reviews conducted for the 2016 revision of the treatment guidelines for drug-resistant TB²

PICO	Characteristics of review	Ref.
1	Systematic review (SR) & study-level meta-analysis for effect of 2 nd line drugs in MDR-TB treatment	(46),(47)
1	SR & individual patient data (IPD) meta-analysis for effect of 2 nd line drugs in MDR-TB treatment	(41)
1	SR & individual patient data (IPD) meta-analysis for the effect of 2 nd line drugs in MDR-TB treatment in children	unpublished
2	SR & study-level meta-analysis for effect of different regimens in isoniazid-resistant TB	(70)
2	SRs for treatment of <i>M. bovis</i> disease	unpublished
3	Meta-analysis of shorter MDR-TB regimens (IPD + aggregated data)	(71)
4	SR for delay to start of MDR-TB treatment	(50)
4	SR for the effect of surgery on MDR-TB patient outcomes	(49)
4	Individual patient data meta-analysis for the effect of surgery on MDR-TB patient outcomes	(48)

IPD=individual patient data meta-analysis; **MDR-TB**=multidrug-resistant TB ; **PICO**=Population, Intervention, Comparator, Outcomes; **SR**=systematic review

² See (27),(33) for details on the reviews done for bedaquiline and delamanid after May 2016.

Supplementary Table S3. Summary of changes in the evidence-informed recommendations between the 2016 and 2011 guidelines (18),(25)

2011 guidelines (18)	2016 guidelines
<p>Use of rapid diagnostics for rifampicin resistance Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources (conditional recommendation, very low quality evidence)</p>	<p>UPDATED [from (22)] Rapid drug susceptibility testing (DST) of at least rifampicin is recommended in adults and children over conventional testing or no testing at the time of diagnosis of TB (strong recommendation, high certainty in the evidence)</p>
<p>Use of sputum microscopy and culture to monitor response to treatment The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDR-TB during treatment (conditional recommendation, very low quality evidence)</p>	<p>REMAINS VALID³</p>
<p>Use of a shorter MDR-TB treatment regimen⁴ NO SPECIFIC RECOMMENDATION</p>	<p>In patients with rifampicin-resistant or multidrug-resistant TB (MDR/RR-TB) who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens (conditional recommendation, very low certainty in the evidence)</p>
<p>Composition of longer MDR-TB treatment regimens In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, very low quality evidence) In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, very low quality evidence) In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, very low quality evidence) In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (<i>p</i>-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, very low quality evidence)</p>	<p>UPDATED⁵ In patients with MDR/RR-TB, a regimen with at least five effective TB medicines during the intensive phase may be used, including pyrazinamide and four core second-line TB medicines - one chosen from group A, one from group B, and at least two from group C⁶ (conditional recommendation, very low certainty in the evidence). If the minimum of effective TB medicines cannot be composed as given above, an agent from group D2 and other agents from D3 may be added to bring the total to five⁷. In patients with MDR/RR-TB, the regimen may be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence).</p>

³ This recommendation continues to apply and will be revised if a future evidence review conducted for the purpose of updating WHO policy guidance shows such need

⁴ See text for the definition of the shorter MDR-TB treatment regimen, and for other conditions which apply when implementing this recommendation

⁵ In October 2016, the WHO policy on the use of delamanid was revised and the medicine is now also recommended for use in patients aged 6-17 years (21),(27). The WHO policy on the use of bedaquiline remains unchanged (20),(33)

⁶ Group A=levofloxacin, moxifloxacin, gatifloxacin; Group B=amikacin, capreomycin, kanamycin, (streptomycin); Group C=ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine. In children with non-severe disease Group B medicines may be excluded

⁷ Group D2=bedaquiline, delamanid; Group D3=*p*-aminosalicylic acid, imipenem-cilastatin, meropenem, amoxicillin-clavulanate, (thioacetazone)

2011 guidelines (18)	2016 guidelines
<p>Composition of conventional MDR-TB treatment regimens (continued) In the treatment of patients with MDR-TB, four second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase (conditional recommendation, very low quality evidence)</p>	<p>UPDATED (as above)</p>
<p>Treatment of patients with rifampicin-resistant TB NO SPECIFIC RECOMMENDATION</p>	<p>Any patient – child or adult – with RR-TB in whom isoniazid resistance is absent or unknown may be treated with a recommended MDR-TB regimen, either a shorter MDR-TB regimen, or if this cannot be used, a longer MDR-TB regimen to which isoniazid is added.</p>
<p>Duration of conventional MDR-TB treatment regimens In the treatment of patients with MDR-TB, an intensive phase of 8 months is suggested for most patients, and the duration may be modified according to the patient’s response to therapy (conditional recommendation, very low quality evidence).</p> <p>In the treatment of patients newly diagnosed with MDR-TB (i.e. not previously treated for MDR-TB), a total treatment duration of 20 months is suggested for most patients, and the duration may be modified according to the patient’s response to therapy (conditional recommendation, very low quality evidence).</p>	<p>REMAINS VALID³</p>
<p>Start of antiretroviral therapy with MDR-TB treatment Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment (strong recommendation, very low quality evidence).</p>	<p>REMAINS VALID³</p>
<p>Use of surgery as part of MDR-TB treatment NO SPECIFIC RECOMMENDATION</p>	<p>In patients with MDR/RR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen (conditional recommendation, very low certainty in the evidence).</p>
<p>Models of MDR-TB care (ambulatory/hospitalization) Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization (conditional recommendation, very low quality evidence).</p>	<p>REMAINS VALID³</p>

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